Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Management of indirect neonatal hyperbilirubinemia.

Bibliographic Source(s)

University of Michigan Health System. Management of indirect neonatal hyperbilirubinemia. Ann Arbor (MI): University of Michigan Health System; 2017 Oct. 19 p. [49 references]

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group
YES	Methodologist Involvement
	Patient and Public Perspectives

	Use of a Systematic Review of Evidence
▮▮▮▮▮	Search Strategy
▮▮▮▮▮	Study Selection
▮▮▮▮▯	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▯▯	Grading the Quality or Strength of Evidence
▮▮▮▯▯	Benefits and Harms of Recommendations
▮▮▮▮▯	Evidence Summary Supporting Recommendations
▮▮▯▯▯	Rating the Strength of Recommendations
▮▮▮▮▯	Specific and Unambiguous Articulation of Recommendations
▮▯▯▯▯	External Review
▮▮▮▮▮	Updating

Recommendations

Major Recommendations

Note from the University of Michigan Health System (UMHS) and the National Guideline Clearinghouse (NGC): The following guidance was current as of October 2017. Because UMHS occasionally releases minor revisions to its guidance based on new information, users may wish to consult the original guideline document for the most current version.

Note from NGC: The following key points summarize the content of the guideline. Refer to the original guideline document for additional information.

The strength of recommendation (I-III) and levels of evidence (A-E) are defined at the end of the "Major Recommendations" field.

Key Points

Prevention

Feed newborns, starting at birth, at least 8 times per day. Feedings should be based on feeding cues with attempts at least every 3 hours.

Continue breastfeeding even if feeding difficulties arise. In certain circumstances, expressed breast milk or formula supplementation may be warranted. Discourage discontinuation of breastfeeding, even for diagnostic purposes in the setting of suspected breast-milk jaundice.

Feeding supplementation is not indicated for sleepy neonates during first 24 to 48 hours, unless signs of dehydration, or weight loss more than the 95th percentile per the newborn weight tool (NEWT).

Feeding recommendations are not relevant if a patient is critically ill and enteral feeds are being

withheld.

Diagnosis

The approach to diagnosing hyperbilirubinemia will differ depending on whether it is detected via screening during the birth hospitalization (see Figure 1 in the original guideline document) or later in follow-up (see Figure 2 in the original guideline document).

History

Assess all newborns for risk factors for developing hyperbilirubinemia (see Table 1 in the original guideline document).

Bilirubin Measurement

A total bilirubin (total serum bilirubin [TSB] or transcutaneous bilirubin [TcB]) level should be measured on all newborns prior to discharge *[I-C]*.

Choose appropriate test for bilirubin levels (see Table 5 in the original guideline document)

If TSB is indicated, the first level should be fractionated to rule out direct hyperbilirubinemia. Subsequent measurements can be total bilirubin alone.

The first measurement should be obtained at 16 to 24 hours of life *[I-C]*.

Discharge prior to 16 hours of life is strongly discouraged. If extenuating circumstances result in the discharge of a neonate prior to 16 hours of life, appropriate follow-up for evaluation of hyperbilirubinemia should be arranged.

Total bilirubin levels should be plotted on the hour-specific nomogram to direct follow up (see Figures 4 and 5 in the original guideline document). If point of care (POC) bilirubin is obtained in the outpatient setting, consider that serum measurements can be 10% higher when interpreting the results.

Further Investigation into Underlying Etiology

Investigation into rarer causes of hyperbilirubinemia is recommended in certain circumstances (see Table 4 in the original guideline document).

Risk Stratification

Use risk stratification (lower, medium, or higher risk ([see Table 3 in the original guideline document]) to determine phototherapy and exchange-transfusion thresholds. To risk stratify, combine gestational age (GA) with presence of neurotoxicity risk factors (see Table 1 in the original guideline document) *[I-D]*.

Treatment

For overview, see Figure 3 in the original guideline document.

Decision to admit to the hospital and treat should be based on TSB *[I-D]*.

Intensive phototherapy can be expected to decrease bilirubin levels by 30% to 40% in 24 hours, with most being in the first 4 to 6 hours. Intensive phototherapy should be initiated in the following circumstances:

- When total bilirubin is at or above the phototherapy treatment threshold based on hour-specific nomograms (see Figure 4 in the original guideline document)
- When TSB rate of rise is greater than 0.2 mg/dL/hour and TSB is predicted to cross treatment threshold prior to next evaluation *[I-D]*

There is lack of evidence to support the routine use of home phototherapy when the bilirubin level is at, near, or above the treatment threshold. However, home phototherapy can be considered when bilirubin is 0-2 mg/dL below the treatment threshold at discharge from the birth hospitalization or in the outpatient

setting in the following circumstances:

- Neonates who feed well, appear well, and have close follow up arranged
- Neonates with no neurotoxicity risk factors (low risk or medium risk based on gestational age alone) *[III-C]*
- Neonates without prior history of intensive phototherapy treatment

When bilirubin values are at or near exchange transfusion values:

- Maximize surface area exposed to phototherapy by removing unnecessary clothing (minimal/no diaper)
- Use highly reflective materials to surround the neonate to increase surface area exposed and irradiance
- Use multiple light sources (measure irradiance at various sites)
- Consider adjunctive therapies, including intravenous immunoglobulin (IVIG) and IV hydration
- Notably, turning baby from prone to supine in an alternating fashion has not been shown to be efficacious

For most neonates, routine IV supplementation is not warranted. However, for neonates with severe hyperbilirubinemia, IV fluid administration may be useful and is recommended.

Use of IVIG may be useful in Rh or ABO disease.

- Use should be restricted to select neonates in the neonatal intensive care unit (NICU) with high bilirubin values or rapid rate of rise (at high risk for exchange transfusion).
- Neonates should be monitored closely.
- Dose 0.5g/kg over 2 hours, repeat as clinically indicated.

An exchange transfusion should be considered when a serum bilirubin value surpasses the applicable American Academy of Pediatrics (AAP) recommended threshold value (see Figure 5 in the original guideline document).

Monitoring

Following the initiation of phototherapy, only serum bilirubin (TSB) levels are recommended.

Stop phototherapy once serum bilirubin has fallen to a level at least 3 mg/dL below the phototherapy threshold.

Rebound levels at 6 hours are not predictive of subsequent repeat phototherapy.

If treated prior to initial hospitalization discharge (post-delivery), consider repeat TSB 24 hours after discontinuation of phototherapy. This can be done as an outpatient.

If preterm, direct antiglobulin test (DAT)+, or treated after readmission and serum bilirubin is greater than 14, recheck TSB 12 to 24 hours after discontinuation of phototherapy. This can be done as an outpatient. (If bilirubin is ≤14, routine repeat TSB is not indicated in all neonates.)

When treating with exchange transfusion, recheck bilirubin every 4 to 6 hours, depending on the rate of decline.

A neonate being treated with home phototherapy (fiber optic blanket, Bili Blanket) should have a TSB checked:

- Every 24 to 48 hours if the neonate is low risk
- Every 24 hours if the neonate is medium risk and has no neurotoxicity risk factors

Discharge should not be delayed to obtain a rebound bilirubin level. Rebound levels can be checked as an outpatient when indicated.

Follow-up

Timing and frequency of follow up after birth hospitalization should be influenced by risk of development of severe hyperbilirubinemia. This can be determined by risk factors for development of severe hyperbilirubinemia (see Table 2 in the original guideline document) as well as plotting TcB or TSB on the Bhutani nomogram (see Appendix 1 in the original guideline document).

For those at higher risk, follow up should occur 1 day following birth hospitalization discharge

After hospital discharge from phototherapy, primary care physician (PCP) follow-up should be arranged within 24 hours, or 48 hours when no serum bilirubin recheck is required (i.e., discharge bilirubin <14).

Phototherapy Techniques

Fiberoptic Phototherapy Blanket

The fiber optic blanket should be applied next to the neonate's skin. The neonate may wear a diaper. The parents should swaddle the neonate with the fiber optic blanket next to the skin to avoid hypothermia. Feeding can continue with the blanket next to the neonate's skin. If necessary, to optimize feeding, the neonate may be removed from the blanket for up to 30 minutes every 2 to 3 hours.

Inpatient Phototherapy

Babies receiving inpatient phototherapy should receive "intensive" phototherapy *[I-C]*.

For the majority of term neonates, phototherapy using a single overhead LED light source will provide intensive phototherapy and will be sufficient.

Phototherapy using a single overhead LED light source and fiberoptic blanket may be indicated when the serum bilirubin value is:

Rising more than 0.5 mg/dl/hour
Within 3 mg/dl below the exchange transfusion threshold
Fails to respond to initial phototherapy

Use of 2 angled overhead lights, a fiberoptic blanket, and white sheets as a reflective surface may be indicated when bilirubin is at or above the exchange transfusion threshold. This is done in the NICU.

Body surface area exposed and continuity of therapy (i.e., minimizing interruptions) will influence efficacy.
Irradiance should be measured regularly.
There is a lack of evidence to support the use of fiberoptic blanket alone.
When neonates are not considered high risk for exchange transfusion, phototherapy can be temporarily halted to allow for bonding and breastfeeding.

Definitions

Levels of Evidence

Systematic reviews of randomized controlled trials with or without meta-analysis
Randomized controlled trials
Systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control)
Individual observational studies (case study/case series)
Expert opinion regarding benefits and harm

Strength of Recommendation

Generally should be performed
May be reasonable to perform
Generally should not be performed

Clinical Algorithm(s)

The following algorithms are provided in the original guideline document:

- Birth Hospitalization
- Outpatient Hyperbilirubinemia
- Hyperbilirubinemia Treatment

Scope

Disease/Condition(s)

Indirect neonatal hyperbilirubinemia

Guideline Category

Diagnosis

Evaluation

Management

Prevention

Risk Assessment

Treatment

Clinical Specialty

Critical Care

Family Practice

Gastroenterology

Internal Medicine

Pediatrics

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To create an evidence-based standard for the management of neonates with indirect hyperbilirubinemia across all care settings (newborn nursery, intensive care units, general inpatient service, home care, primary care, and emergency department) that provides appropriate care to patients, reduces unnecessary

diagnostic tests and interventions, and improves patient outcomes

Target Population

Neonates less than 8 days of life *and* 35 weeks gestation or more

Note: This guideline does not include the management of neonatal direct hyperbilirubinemia or hyperbilirubinemia in patients greater than 8 days of age. This guideline excludes premature neonates born prior to 35 weeks gestation.

Interventions and Practices Considered

Diagnosis/Evaluation

- Assessment of history for risk factors
- Bilirubin measurement
  - Total serum bilirubin (TSB)
  - Transcutaneous bilirubin (TcB)
- Further investigation into underlying etiology, as necessary
- Risk stratification

Treatment/Management

- Admission to hospital based on TSB
- Initiation of intensive phototherapy
  - Single or double overhead LED lights
  - Fiberoptic phototherapy blanket
  - White sheets as reflective surface
- Home phototherapy (i.e., fiberoptic phototherapy blanket)
- Intravenous (IV) supplementation for severe hyperbilirubinemia
- Intravenous immunoglobulin (IVIG)
- Exchange transfusion
- Monitoring of TSB levels
- Discontinuation of phototherapy, as indicated
- Monitoring of rebound levels
- Follow-up evaluation with primary care physician (PCP)

Prevention

- Exclusive breastfeeding from birth, at least 8 times per day
- Discouraging discontinuation of breastfeeding
- Feeding supplementation, as indicated

Major Outcomes Considered

- Sensitivity/specificity of diagnostic tests
- Cure rate
- Infection rate
- Time to improvement
- Complications
- Mortality
- Adverse events

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Strategy for Literature Search

Within the Medline (Ovid) database, the following search strategy was used.

exp *hyperbilirubinemia, neonatal/
*hyperbilirubinemia/ or *jaundice/ or *kernicterus/
limit 2 to "all infant (birth to 23 months)"
(neonatal or neonate* or infant* or newborn*).ti.
2 and 4
exp animals/ not (exp animals/ and humans/)
5 not 6
1 or 3 or 7
limit 8 to (english language and yr="2004 -Current")

The search was not focused on indirect hyperbilirubinemia because the retrieval was very small. The Main search retrieved 1,213 references. When the search hedges for Guidelines, Clinical Trials, and Cohort Studies were added, the base results are as follow:

Neonatal Hyperbilirubinemia - Guidelines, total results were 35
Neonatal Hyperbilirubinemia - Clinical Trials, total results were 125
Neonatal Hyperbilirubinemia - Cohort Studies, total results were 262

The MEDLINE In-Process database was also searched using the strategy in the methodological appendix (see the "Availability of Companion Documents" field). The search retrieved 100 documents. The results with the hedges applied are:

Guidelines, total results were 2
Clinical Trials, total results were 11
Cohort Studies, total results were 21

Within the Cochrane Database of Systematic Reviews, 6 reviews were found using the strategy in the search strategies document. The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle.

Search details and evidence tables are available in the methods companion (see the "Availability of Companion Documents" field).

Number of Source Documents

The search identified a total of 462 potentially relevant publications. The review process resulted in 91 studies identified as presenting best evidence on a topic.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence

Systematic reviews of randomized controlled trials with or without meta-analysis
Randomized controlled trials
Systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control)
Individual observational studies (case study/case series)
Expert opinion regarding benefits and harm

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Best Evidence Identified and Organized into Evidence Tables

The best evidence for the current guideline is synthesized into 16 evidence tables reflecting the primary questions posed in the literature review. These tables include a total of 91 publications. The tables themselves are contained in Section VI of the Methodological Appendix (see the "Availability of Companion Documents" field), and present the synthesis of the best evidence identified.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Guideline recommendations were based on prospective randomized controlled trials (RCTs) if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size. The "strength of recommendation" for key aspects of care was determined by expert opinion.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendation

Generally should be performed
May be reasonable to perform
Generally should not be performed

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Health System to which the content is most relevant: Family Medicine, Pediatrics, Pediatric Emergency Medicine, Pediatric Internal Medicine. The Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers endorsed the final version.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for selected recommendations (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Exclusive breastfeeding is recommended during first 6 months of life, as all-cause mortality is less in exclusive breast fed neonates.
- Compared with selective testing, universal screening reduces total blood draws and phototherapy rates.
- Intensive phototherapy can be expected to decrease bilirubin levels by 30% to 40% in 24 hours, with most being in the first 4 to 6 hours. Phototherapy is in general effective at decreasing serum bilirubin values (TSB) and preventing the need for exchange transfusion.
- A randomized controlled trial (RCT) found supplementing with intravenous (IV) fluids for the first 8 hours of phototherapy followed by enteral supplementation was associated with fewer exchange transfusions. Another RCT of 100 well appearing neonates found the mean decrease in transcutaneous bilirubin (TcB) at 24 hours of phototherapy was greater with IV supplementation.
- A single RCT showed the use of albumin priming prior to exchange transfusion (1 mg/kg, 1 hour before exchange transfusion) resulted in lower TBS values at 12 hours and a shorter length of stay for neonates receiving albumin.

Potential Harms

- Exclusive breastfeeding is strongly associated with an increased risk of hyperbilirubinemia, however, the hyperbilirubinemia appears to be primarily the result of less effective breastfeeding.
- Though there is a paucity of evidence phototherapy has risk, melanocytic nevus development is a worry. Blue light can induce retinal photoreceptor degeneration in rats and in mammals.
- Potential adverse sequelae of exchange transfusion include leukopenia, thrombocytopenia, hypocalcemia, hypernatremia, and bacteremia.
- False negative and false positive results of tests

Contraindications

Contraindications

- Home phototherapy should not be used in neonates with neurotoxicity risk factors, nor those who have required intensive phototherapy.
- Do not use transcutaneous bilirubin (TcB) if phototherapy has been initiated.

Qualifying Statements

Qualifying Statements

These guidelines should not be construed as including all proper methods of care or excluding other acceptable methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding any specific clinical procedure or treatment must be made by the physician in light of the circumstances presented by the patient.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

University of Michigan Health System. Management of indirect neonatal hyperbilirubinemia. Ann Arbor (MI): University of Michigan Health System; 2017 Oct. 19 p. [49 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 Oct

Guideline Developer(s)

University of Michigan Health System - Academic Institution

Source(s) of Funding

The development of this guideline was funded by the University of Michigan Health System.

Guideline Committee

Hyperbilirubinemia Guideline Team

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Financial Disclosures/Conflicts of Interest

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Relevant personal financial relationships with commercial entities: None.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the University of Michigan Health System Web site .

Availability of Companion Documents

The supplemental methodological appendix is available from the University of Michigan Health System (UMHS) Web site

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on March 27, 2018. The information was verified by the guideline developer on May 3, 2018.

This NEATS assessment was completed by ECRI Institute on April 4, 2018. The information was verified by the guideline developer on May 3, 2018.

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